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EXAMINER
JONES, DAMERON L

ART UNIT	PAPER NUMBER
1616	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/910,639	Applicant(s) VALLERA ET AL.	
	Examiner D. L. Jones	Art Unit 1616	

-- The MAILING DATE of this communication app ars on the c ver sh et with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/8/02; 8/13/02; 11/18/02; and 3/31/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *1-17,19,25 and 30-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20-24 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5,&10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

APPLICANT'S INVENTION

1. Applicant's invention is directed to radiolabeled immunotoxins and uses thereof.

Note: Claims 1-39 are pending.

RESPONSE TO APPLICANT'S ELECTION

2. Applicant's election without traverse of Group III (claims 18-29) directed to a method of administering a radiolabeled immunotoxin as set forth in independent claim 18 in Paper No. 13, filed 3/31/03, is acknowledged. Since the election was made without traverse the restriction requirement is deemed proper and is therefore made FINAL. Likewise, it is noted that Applicant elected a species wherein the toxic domain is diphtheria toxin; the targeting molecule is Her-2/Neu; and the radionuclide species is 64Cu.

Notes: Initially, Applicant's elected species was searched. However, since no prior art was found which could be used to reject the claims, the search was expanded to diphtheria toxin (toxic domain), any radionuclide, and anti-CD3 sFv (targeting moiety). The search was not further expanded because prior art was found which could be used to reject Applicant's claims.

WITHDRAWN CLAIMS

3. Claims 1-17, 19, 25, and 30-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention/species.

DOUBLE PATENTING

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 18, 20-23, 26, 27, and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,001,329. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of killing/treating pathogenic cells wherein a composition comprising a

radiolabeled immunotoxin having a toxic domain, a targeting moiety, and a radionuclide are utilized. The claims differ in that those of the instant invention specifically disclose that the targeting moiety is sFv antibody fragment that binds to a target molecule.

112 REJECTIONS (First Paragraph)

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 18, 20-24, and 26-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing target cells (e.g., cancer cells) and imaging a subject, does not reasonably provide enablement for neither all other methods wherein a radiolabeled immunotoxin having a targeting domain that is a sFv antibody fragment or for all pathogenic cell diseases is administered to a subject nor for all known pathogenic diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are several guidelines when determining if the specification of an application allows the skilled artisan to practice the invention without undue experimentation. The factors to be considered in determining what constitutes undue experimentation were affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1986)). These factors are the quantity of experimentation; the amount of direction or guidance presented in the specification; the presence or absence of working examples;

the nature of the invention; the state of the prior art; the level of skill of those in the art; predictability or unpredictability of the art; and the breadth of the claims. In particular, the specification fails to enable the skilled artisan to practice the invention without undue experimentation wherein any method other than killing a target cell or imaging a subject are utilized. In addition, the specification fails to enable the skilled artisan to practice the invention without undue experimentation wherein any pathogenic disease other than cancer is utilized.

The disclosure of claims 18, 20-24, and 26-29 is drawn to a method comprising identifying a subject with a pathogenic disease and administering an radiolabeled immunoconjugate. While a skilled artisan would be motivated to select a method of killing or imaging or cancer as the pathogenic disease, the artisan would not know what other methods or pathogenic diseases Applicant is referring to which would be compatible with the instant invention. Hence, a skilled artisan in the art would not be able to readily ascertain the unlimited number of methods or pathogenic diseases useful with known or hypothetical radiolabeled immunotoxins that would have the same results as those obtained in a method of killing and imaging involving cancer cells. Thus, the skilled artisan would be forced to randomly test various methods using the radiolabeled immunoconjugate and pathogenic diseases in order to determine which methods and pathogenic diseases yield similar results as that obtained when the radiolabeled immunotoxin for killing cancer cells or imaging a subject. Furthermore, the amount of guidance present in the specification fails to present the necessary instruction to determine what methods and pathogenic diseases are encompassed by the claims.

The specification does not provide guidance as to any other methods and pathogenic diseases, other than those previously stated, which yield similar/same results as those obtained from killing a cancer cell or imaging a subject, nor does the

specification disclose specific characteristics/conditions necessary for obtaining desired results. In addition, the specification fails to provide guidance as to how any one should modify a method to obtain a certain response or which pathogenic diseases to generate similar data. No working examples are provided to provide such missing information. Without such information, one skilled in the art could not predict which methods out of the vast number of known and hypothetical methods are useful with a radiolabeled immunotoxins are encompassed by Applicant's phrase "a method". Likewise, a skilled artisan could not predict which pathogenic cell disease out of the vast number of known pathogenic diseases are encompassed in the instant invention. Therefore, due to the lack of guidance and the amount of experimentation required to identify any methods and pathogenic diseases that compatible with the instant invention, methods other than killing cancer cells and imaging a subject are not properly enabled by the instant specification.

112 REJECTIONS (Second Paragraph)

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 18, 20-24, and 26-29 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 and 20-24: The claims as written are ambiguous because it is unclear what method Applicant is claiming that is compatible with the instant invention.

Claims 18, 20, 21, and 26-29: The claims as written are ambiguous because it is unclear what pathogenic cell disease(s) the claims are directed to.

102 REJECTIONS

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 18, 20, 21, 26, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Vallera et al (Blood (1996), pages 2342-2353).

Vallera et al disclose anti-graft versus host disease (GVHD) effect of diphtheria toxin 390 (DT-390) antiCD3sFv, a single chain Fv fusion immunotoxin that specifically targets the CD3 epsilon moiety of the T-cell receptor (see entire document). In addition, Vallera et al disclose (1) mice received 2 micrograms of immunotoxin on a daily basis for six days (see abstract; page 2345, 'Fusion toxin administration'; page 2349 'Effect of DT390-anti-CD3sFv administration on in vivo GVHD'). (2) The immunotoxin was radiolabeled with 125I (page 2345, 'Pharmacokinetics'; page 2350, Figure 8).

Thus, both Vallera et al and Applicant disclose a method of administering a radiolabeled immunotoxin comprising a toxic domain, a targeting domain that is a sFv antibody fragment that binds to a target molecule, and a radionuclide to a subject having a pathogenic condition.

103 REJECTIONS

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 18, 20-23, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vallera et al (Blood (1996), pages 2342-2353) in view of Goldenberg (US Patent No. 5,332,567).

Vallera et al (see discussion above) fail to disclose other methods in which an radiolabeled immunotoxin is administered to a subject. Also, Vallera et al fail to disclose other possible radionuclides which may be conjugated to the DT-390-anti-CD3sFv complex.

Goldenberg discloses the detection, imaging, and treatment of infections using immunoconjugates comprising and antibody conjugate (see entire document, especially, abstract). The immunoconjugates comprise an immunoreactive component having at least one substantially monospecific antibody or antibody fragment conjugated to at least one diagnostic or therapeutic agent, wherein the antibody fragment binds to an epitope of the pathogen or of a pathogen-associated antigen (column 2, lines 47-55). The invention of Goldenberg also resolves many of the problems involved in the treatment of infections that are refractive to conventional drug therapy by using very specific antibodies against microbial or parasitic antigens in order to target an effective

radionuclide and/or chemical agent resulting in selective killing of the pathogen (column 3, lines 41-47). The immunoconjugates are also effective diagnostic agents for scintigraphic imaging or magnetic resonance imaging of infection sites which enable a treating physician to evaluate a patients level and stage of infection and design and monitor treatment protocols (column 3, lines 59-64). The imaging agents may comprise bispecific, trispecific, or polyspecific antibody/antibody fragment conjugates that optionally comprise an imaging radioisotope or paramagnetic species (column 4, lines 62-66).

Also, Goldenberg discloses the value of conjugating antibodies with radioisotopes and/or drugs or toxins to achieve target detection, imaging, and therapy of infection (column 6, lines 57-61; column 10, lines 7-26; column 13, lines 18-22; column 16, lines 5-45; column 19-28). The immunoconjugates may be labeled with metals such as Dy, Gd, or Mn to name a few (column 11, lines 6-23; column 18, lines 17-25). The methods and compositions of Goldenberg are effective in the treatment of acquired immune deficiency syndrome and similar conditions (column 18, lines 48-57; column 19, lines 30-35).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Vallera et al using the teachings of Goldenberg and use a radiolabeled immunotoxin in various methods and conjugate various radionuclides to the DT-390-antiCD3sFv complex because (a) both Vallera et al and Goldenberg disclose the use of immunoconjugates for targeting a diagnostic or therapeutic agent such as detecting, imaging, or treating and infection. (b) Goldenberg

discloses that the immunoconjugate may be labeled with different radioisotopes depending upon the technique used (e.g., imaging, therapy, etc.). Thus, since both references disclose immunoconjugates that may be radiolabeled, the references may be considered to be within the same field of endeavor. Hence, the references are combinable.

14. Claims 18, 20-23, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al (1995), Vol. 270, No. 47, pp. 28037-28401 in view of Goldenberg (US Patent No. 5,332,567).

Thompson et al disclose an immunotoxin comprising anti-CD3sFv-DT390 complex (see entire document, especially, abstract; page 28037, 'Immunotoxins'). Thompson et al fail to disclose an in vivo method wherein the compositions is administered to a subject and the attachment of various radionuclides to the anti-CD3 single chain immunoconjugate.

Goldenberg (see discussion above).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Thompson et al using the teachings of Goldenberg and use the immunotoxin conjugate in vivo for various methods such as detecting, imaging, or treating infection because (a) On page 28040 (forth line from both of page, column 1) of Thompson et al, it is disclosed the experiments of Thompson et al were designed to mimic the in vivo situation. (b) Goldenberg discloses that the immunoconjugate may be labeled with different radioisotopes depending upon the

technique used (e.g., imaging, therapy, etc.). Thus, since both references disclose immunoconjugates, the references may be considered to be within the same field of endeavor. Hence, the references are combinable.

SEQUENCE RULES

15. Applicant needs to comply with the sequence rules since there are sequences present in the application (e.g., see page 25, line 14; page 15, line 16; page 37, line 23; page 38, lines 6-8, etc.). Please review the attached notice regarding compliance with the sequence rules.

COMMENTS/NOTES

16. It should be noted that no prior art has been cited against claim 24. Claim 24 is distinguished over the prior art of record because the prior art neither anticipates nor renders obvious an immunotoxin comprising diphtheria toxin, 64Cu, and Her-2/Neu (Applicant's elected species). However, Applicant MUST address the 112 rejections above.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose' Dees can be reached on (703) 308- 4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1616

June 13, 2003

NOTICE TO COMPLY WITH THE SEQUENCE RULES

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN THREE MONTHS (see MPEP 2421.03) FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to the Group 1600 fax machine at (703) 308-4556. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30; November 15, 1989.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Monday - Friday, 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose' Dees can be reached on (703) 308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit ~~1619~~ 1616

June 13, 2003

Application No. 09/910,639

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached marked-up copy of the "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7. Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

Please return a copy of this notice with your response.